Letters

COMMENT & RESPONSE

Acetaminophen in Pregnancy and Adverse Childhood Neurodevelopment

To the Editor The article by Stergiakouli et al[1] is the latest addition to studies reporting on childhood neurodevelopment following in utero exposure to acetaminophen, studies that generate much public attention, debate, and controversy.[2-4] We believe that the clinical conclusions highlighted by the authors are insufficiently substantiated by their findings.

While adjusted point estimates of risk ratios for Strength and Difficulties Questionnaire (SDQ) total difficulty score and conduct problem score remained about the same, the authors' statement that "inclusion of covariates did not change the RRs [risk ratios]..."[1] is inaccurate. Risk ratio is attenuated for hyperactivity score; the association with emotional symptoms score vanishes, and lower-bound confidence limits barely eclipse 1 for significant associations. It would require about 50 pregnant women to receive acetaminophen in the second trimester of pregnancy for 1 additional child to score greater than 17 on a parent-assessed Strength and Difficulties Questionnaire at the age of 7 years.[1] We are unconvinced as to the clinical significance thereof. The binary exposure data preclude analysis of dose and duration, both of which are important to establish and substantiate a biologically plausible rationale. There are no data on concomitant drug exposure, which may represent an important confounder.

In this and similar studies, parent-assessed questionnaires are used uncritically as principal end points for estimation of childhood neurodevelopment.[2,4] Such questionnaires are typically developed and validated as a parental screening tool to identify children at risk.[5] The Strength and Difficulties Questionnaire was not validated as a quantifiable end point that accurately translates objective childhood neurodevelopment into a continuous or dichotomous scale measurement, thereby allowing for statistical quantitative analyses. The resulting statistically significant risk ratios/odds ratios or regression β-slope values are in turn assigned clinical significance. We believe this approach compromises the extent to which meaningful clinical implications can be allowed.[5] A 2016 study used the reference approach of blinded Bayley III scores as assessed by trained health care professionals.[3] No difference in the primary end point, attention-deficit/hyperactivity disorder *DSM-IV* total symptoms score, among exposed and unexposed was found, although a stratified analysis produced a small inference with respect to hyperactivity/impulsivity symptoms.

Unless robust, validated prospective outcome and exposure data are at hand, we suggest that researchers resist the temptation to address such controversial hypotheses. We are concerned about the unsubstantiated uncertainty and anxiety that the publication of these studies creates in pregnant women. We invite interested authors to spend a day in a teratology information center following publication of their study.

Per Damkier, MD, PhD
Anthony R. Scialli, MD, PhD
Shari I. Lusskin, MD

Author Affiliations: Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Funen, Denmark (Damkier); Reproductive Toxicology Center, Washington, DC (Scialli); Departments of Psychiatry, Obstetrics, Gynecology, and Reproductive Science, Icahn School of Medicine at Mount Sinai, New York, New York (Lusskin).

Corresponding Author: Per Damkier, MD, PhD, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Sdr Boulevard 29, Odense, Funen 5000 C, Denmark (pdamkier@health.sdu.dk).

Published Online: February 13, 2017. doi:10.1001/jamapediatrics.2016.5049

Conflict of Interest Disclosures: Dr Scialli declares past consulting for Cadence Pharmaceuticals Inc. No other disclosures are reported.

1. Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatr*. 2016;170(10):964-970.

2. Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol*. 2013;42(6):1702-1713.

3. Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. *Int J Epidemiol*. 2016;(June):dyw115.

4. Liew Z, Ritz B, Rebordosa C, Lee P-C, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr*. 2014;168(4):313-320.

5. Damkier P, Pottegård A, dePont Christensen R, Hallas J. Annotations and reflections: pregnancy and paracetamol: methodological considerations on the study of associations between in utero exposure to drugs and childhood neurodevelopment. *Basic Clin Pharmacol Toxicol*. 2015;116(1):2-5.